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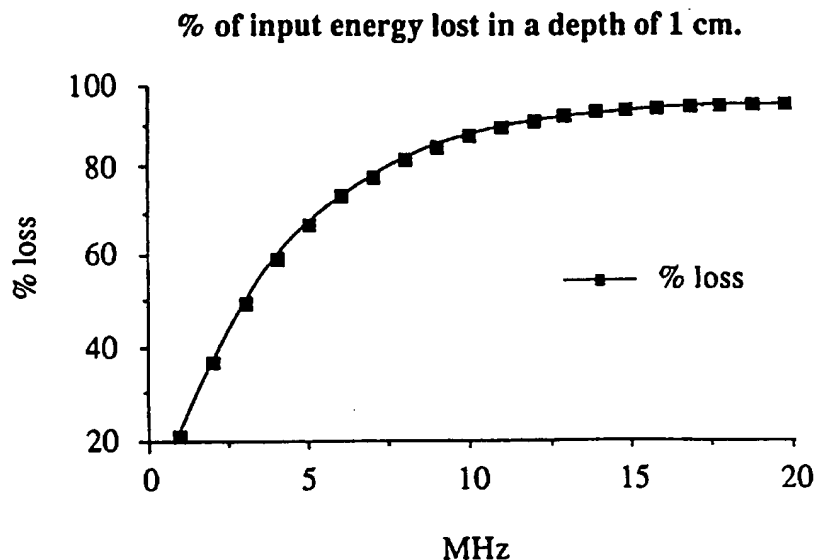
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(54) **AMELIORATION PAR ULTRASONS DE LA LIBERATION DES
MATIERES DANS ET A TRAVERS LA PEAU**

(54) **ULTRASOUND-ENHANCED DELIVERY OF MATERIALS
THROUGH THE SKIN**



(57) Une méthode pour accroître la perméabilité de la peau ou d'une autre membrane biologique à une substance, comme un médicament, est divulguée. Dans cette méthode, le médicament est administré à l'aide d'ultrasons dont la fréquence est supérieure à environ 10 MHz. La méthode peut également être utilisée de concert avec des agents facilitant la perméation chimique et/ou avec l'iontophorèse.

(57) A method for enhancing the permeability of the skin or other biological membrane to a material such as a drug is disclosed. In the method, the drug is delivered in conjunction with ultrasound having a frequency of above about 10 MHz. The method may also be used in conjunction with chemical permeation enhancers and/or with iontophoresis.

ULTRASOUND-ENHANCED PERMEABILITY OF BIOLOGICAL MEMBRANES

This invention relates to a method of enhancing the rate of permeation through a biological membrane, for example the stratum corneum of an individual of materials using high frequency ultrasound.

This method of enhanced permeability can be used for sampling of physiologic material by extraction through the membrane of a diagnostic quantity of the material.

Background

Skin is a structurally complex, relatively impermeable membrane. Molecules moving through intact skin into the environment must penetrate the stratum corneum and any material on its surface. In addition, these molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon. However, it is the stratum corneum, a layer approximately 5-15 micrometers thick over most of the body, which presents the primary barrier to extraction of the physiologic material beneath membranes. It is believed to be the high degree of keratinization within its cells as well as their dense packing and cementation by ordered, semicrystalline lipids which create in many cases a substantially impermeable barrier.

Various methods have been used to increase skin permeability, and in particular to increase the permeability of the stratum corneum. The primary focus has been on the use of chemical enhancers, i.e., a penetration enhancing agent (or "permeation enhancer"). While such compounds are effective in increasing the rate at which physiological material can be extracted through the skin, there are drawbacks with many permeation enhancers which limit their use. For example, many permeation enhancers are associated with deleterious effects on the skin (e.g., irritation).

Iontophoresis has also been used to increase the permeability of skin to drugs, and involves the application of an external electric field. While permeation enhancement via iontophoresis has, as with chemical enhancers, been effective, there are problems with control of drug delivery and the degree of irreversible skin damage induced by the transmembrane passage of current.

The presently disclosed and claimed method involves the use of ultrasound to decrease the barrier function of the stratum corneum. "Ultrasound" is defined as mechanical pressure waves with frequencies above 20,000 Hz (see, e.g., H. Lutz et al., Manual of Ultrasound: 1. Basic Physical and Technical Principles (Berlin: Springer-Verlag, 1984)).

As discussed by P. Tyle et al. in Pharmaceutical Research 6(5):355-361 (1989), drug penetration achieved via "sonophoresis" (the movement of drugs through skin under the influence of an ultrasonic perturbation; see D.M. Skauen and G.M. Zentner, Int. J. Pharmaceutics 20:235-245 (1984)), is believed to result from thermal, mechanical and chemical alteration of biological tissues by the applied ultrasonic waves. Unlike iontophoresis, the risk of skin damage appears to be low.

Applications of ultrasound to membrane permeability have been discussed in the literature. See, for example: P. Tyle et al., supra (which provides an overview of sonophoresis); J. Kost et al., Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 16(141):294-295 (1989) (overview of the effect of ultrasound on the permeability of human skin and synthetic membranes); and C. Escoffier et al., Bioeng. Skin 2:87-94 (1986) (in vitro study of the velocity of ultrasound in skin).

In addition to the aforementioned art, U.S. Patents Nos. 4,767,402 and 4,780,212 to Kost et al. relate specifically to the use of specific frequencies of ultrasound to enhance the permeability of human skin or a synthetic membrane.

While the application of ultrasound to permeabilize membranes is thus known, results have for the most part been disappointing, i.e., enhancement of skin permeability has been relatively low.

Summary of the Invention

It is accordingly a primary object of the invention to address the aforementioned deficiencies of the prior art by providing a method of enhancing the permeability of biological membranes and thus allowing for an increased rate of delivery of materials therethrough.

According to a first aspect of the invention there is provided a method for sampling physiologic material present beneath a biological membrane comprising increasing the permeability of the membrane by applying ultrasound having a frequency above 10MHz to a selected area of the biological membrane, at an intensity and for a period of time effective to increase the permeability of the biological membrane and sufficient to enable movement of a diagnostic quantity of the physiologic material through the membrane to a surface thereof and measuring the physiologic material.

Brief Description of the Drawings

In the accompanying drawings:

Figures 1A, 1B and 1C are theoretical plots of energy dissipation within the skin barrier versus frequency of applied ultrasound.

Figures 2, 3 and 4 are graphic representations of the amount of salicylic acid recovered from the stratum corneum after ultrasound treatment at different frequencies.

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Figures 5 and 6 represent the results of experiments similar to those summarized in Figures 2, 3 and 4, but with a shorter treatment time.

5 Figures 7, 8, 9 and 10 are plots of enhancement versus "tape-strip number," as described in the Example.

10 Figure 11 illustrates the effect of ultrasound on the systemic availability of salicylic acid following topical application.

Detailed Description of Preferred Embodiments

15 Before the present method of enhancing the rate of permeation of a material through a biological membrane and enhancing the permeability of membranes using ultrasound are disclosed and described, it is to be understood that this invention is not limited to the particular process steps and materials disclosed herein as such process steps and materials may, of course, vary. It is also to be understood that the terminology used herein is used for purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims.

25 It must be noted that as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a drug" includes mixtures of drugs and their pharmaceutically acceptable salts, reference to "an ultrasound device" includes one or more ultrasound devices of the type necessary for carrying out the present invention, and reference to "the method of administration" includes one or more different methods of administration known to those skilled in the

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art or which will become known to those skilled in the art upon reading this disclosure.

5 In one aspect of the invention, a method is provided for enhancing the permeation of a given material such as a drug, pharmacologically active agent, or diagnostic agent into and/or through a biological membrane on an individual's body surface, which method comprises: (a) contacting the membrane with the chosen
10 material in a pharmacologically acceptable carrier medium; and (b) applying ultrasound of an intensity and for a treatment time effective to produce delivery of the material through the membrane. The material is preferably a drug and it is preferable to obtain a
15 desired blood level of the drug in the individual. The ultrasound is of a frequency and intensity effective to increase the permeability of the selected area to the applied drug over that which would be obtained without ultrasound. The ultrasound preferably has a frequency
20 of more than 10 MHz, and may be applied either continuously or pulsed, preferably continuously. The ultrasound may be applied to the skin either before or after application of the drug medium so long as administration of the ultrasound and the drug medium is
25 relatively simultaneous, i.e., the ultrasound is applied within about 6, more preferably within about 4, most preferably within about 2 minutes of drug application.

The invention is useful for achieving transdermal permeation of pharmacologically active
30 agents which otherwise would be quite difficult to deliver through the skin or other body surface. For example, proteinaceous drugs and other high molecular weight pharmacologically active agents are ideal candidates for transdermal, transmucosal or topical
35 delivery using the presently disclosed method. In an alternative embodiment, agents useful for diagnostic

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purposes may also be delivered into and/or through the body surface using the present method.

5 The invention is also useful as a non-invasive diagnostic technique, i.e., in enabling the sampling of physiologic material from beneath the skin or other body surface and into a collection (and/or evaluation) chamber.

10 The present invention will employ, unless otherwise indicated, conventional pharmaceutical methodology and more specifically conventional methodology used in connection with transdermal delivery of pharmaceutically active compounds and enhancers.

15 In describing the present invention, the following terminology will be used in accordance with the definitions set out below.

20 A "biological membrane" is intended to mean a membrane material present within a living organism which separates one area of the organism from another and, more specifically, which separates the organism from its outer environment. Skin and mucous membranes are thus included.

25 "Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a material such as a pharmacologically active agent, i.e., so as to increase the rate at which the material permeates into and through the skin. The present invention involves enhancement of permeation through the use of ultrasound, and, in particular, through the use of ultrasound having
30 a frequency of greater than 10 MHz.

35 "Transdermal" (or "percutaneous") shall mean passage of a material into and through the skin to achieve effective therapeutic blood levels or deep tissue therapeutic levels. While the invention is

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described herein primarily in terms of "transdermal" administration, it will be appreciated by those skilled in the art that the presently disclosed and claimed method also encompasses the "transmucosal" and "topical" administration of drugs using ultrasound.

"Transmucosal" is intended to mean passage of any given material through a mucosal membrane of a living organism and more specifically shall refer to the passage of a material from the outside environment of the organism, through a mucous membrane and into the organism.

"Transmucosal" administration thus includes delivery of drugs through either nasal or buccal tissue. By "topical" administration is meant local administration of a topical pharmacologically active agent to the skin as in, for example, the treatment of various skin disorders or the administration of a local anaesthetic. "Topical" delivery can involve penetration of a drug into the skin but not through it, i.e., topical administration does not involve actual passage of a drug into the bloodstream.

"Carriers" or "vehicles" as used herein refer to carrier materials without pharmacological activity which are suitable for administration with other pharmaceutically active materials, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with the drug to be administered in a deleterious manner. Examples of suitable carriers for use herein include water, mineral oil, silicone, inorganic gels, aqueous emulsions, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

By the term "pharmacologically active agent" or "drug" as used herein is meant any chemical material

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or compound suitable for transdermal or transmucosal administration which can either (1) have a prophylactic effect on the organism and prevent an undesired biological effect such as preventing an infection, (2) alleviates a condition caused by a disease such as alleviating pain caused as a result of a disease, or (3) either alleviates or completely eliminates the disease from the organism. The effect of the agent may be local, such as providing for a local anaesthetic effect or it may be systemic. Such substances include the broad classes of compounds normally delivered through body surfaces and membranes, including skin. In general, this includes: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta-blockers, and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. By the method of the present invention, both ionized and nonionized drugs may be delivered, as can drugs of either high or low molecular weight.

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Proteinaceous and polypeptide drugs represent a preferred class of drugs for use in conjunction with the presently disclosed and claimed invention. Such drugs cannot generally be administered orally in that they are often destroyed in the G.I. tract or metabolized in the liver. Further, due to the high molecular weight of most polypeptide drugs, conventional transdermal delivery systems are not generally effective. It is also desirable to use the method of the invention in conjunction with drugs to which the permeability of the skin is relatively low, or which give rise to a long lag-time (application of ultrasound as described herein has been found to significantly reduce the lag-time involved with the transdermal administration of most drugs).

By a "therapeutically effective" amount of a pharmacologically active agent is meant a nontoxic but sufficient amount of a compound to provide the desired therapeutic effect. The desired therapeutic effect may be a prophylactic effect, in preventing a disease, an effect which alleviates a system of the disease, or a curative effect which either eliminates or aids in the elimination of the disease.

As noted above, the present invention is a method for enhancing the rate of permeation of a drug through an intact area of an individual's body surface, preferably the human skin. The method involves transdermal administration of a selected drug in conjunction with ultrasound. Ultrasound causes thermal, mechanical and chemical alterations of biological tissue, thereby enhancing the rate of permeation of a given material therethrough.

While not wishing to be bound by theory, applicants propose that the use of higher frequency

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ultrasound as disclosed herein specifically enhances the permeation of the drug through the outer layer of skin, i.e., the stratum corneum, by causing momentary and reversible perturbations within (and thus short-term, reversible reduction in the barrier function of) the layer of the stratum corneum. It will be appreciated by those skilled in the art of transdermal drug delivery that a number of factors related to the present method will vary with the drug to be administered, the disease or injury to be treated, the age of the selected individual, the location of the skin to which the drug is applied, and the like.

As noted above, "ultrasound" is ultrasonic radiation of a frequency above 20,000 Hz. As may be deduced from the literature cited above, ultrasound used for most medical purposes typically employs frequencies ranging from 1.6 to about 10 MHz. The present invention, by contrast, employs ultrasound frequencies of greater than about 10 MHz, preferably in the range of about 15 to 50 MHz, most preferably in the range of about 15 to 25 MHz. It should be emphasized that these ranges are intended to be merely illustrative of the preferred embodiment; in some cases higher or lower frequencies may be used.

The ultrasound may be pulsed or continuous, but is preferably continuous when lower frequencies are used. At very high frequencies, pulsed application will generally be preferred so as to enable dissipation of generated heat.

The preferred intensity of the applied ultrasound is less than about 5.0 W/cm^2 , more preferably is in the range of about 0.01 to 5.0 W/cm^2 , and most preferably is in the range of 0.05 to 3.0 W/cm^2 . The total treatment time, i.e., the period over which drug

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and ultrasound are administered, will vary depending on the drug administered, the disease or injury treated, etc., but will generally be on the order of about 30
5 seconds to 60 minutes, preferably 5 to 45 minutes, more preferably 5 to 30 minutes, and most preferably 5 to 10 minutes. It should be noted that the aforementioned ranges represent suggested, or preferred, treatment times, but are not in any way intended to be limiting.
10 Longer or shorter times may be possible and in some cases desirable. Virtually any type of device may be used to administer the ultrasound, providing that the device is capable of producing the higher frequency ultrasonic waves required by the present method. A
15 device will typically have a power source such as a small battery, a transducer, a reservoir in which the drug medium is housed (and which may or may not be refillable), and a means to attach the system to the desired skin site.

20 As ultrasound does not transmit well in air, a liquid medium is generally needed to efficiently and rapidly transmit ultrasound between the ultrasound applicator and the skin. As explained by P. Tyle et al., cited above, the selected drug medium should
25 contain a "coupling" or "contacting" agent typically used in conjunction with ultrasound. The coupling agent should have an absorption coefficient similar to that of water, and furthermore be nonstaining, nonirritating to the skin, and slow drying. It is clearly preferred that
30 the coupling agent retain a paste or gel consistency during the time period of ultrasound administration so that contact is maintained between the ultrasound source and the skin. Examples of preferred coupling agents are mixtures of mineral oil and glycerine and propylene
35 glycol, oil/water emulsions, and a water-based gel. A

solid-state, non-crystalline polymeric film having the above-mentioned characteristics may also be used. The drug medium may also contain a carrier or vehicle, as defined alone.

5

A transdermal patch as well known in the art may be used in conjunction with the present invention, i.e., to deliver the drug medium to the skin. The "patch", however, must have the properties of the coupling agent as described in the preceding paragraph so as to enable transmission of the ultrasound from the applicator, through the patch, to the skin.

10

As noted earlier in this section, virtually any chemical material or compound suitable for transdermal, transmucosal or topical administration may be administered using the present method. Again, the present invention is particularly useful to enhance delivery of proteinaceous and other high molecular weight drugs.

15

The method of the invention is preferably carried out as follows. The drug medium, i.e., containing the selected drug or drugs in conjunction with the coupling agent and optionally a carrier or vehicle material, is applied to an area of intact body surface. Ultrasound preferably having a frequency greater than about 10 MHz may be applied before or after application of the drug medium, but is preferably applied immediately before application of the drug so as to "pretreat" the skin prior to drug administration.

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It should also be pointed out that the present method may be used in conjunction with a chemical permeation enhancer as known in the art, wherein the ultrasound enables the use of much lower concentrations of permeation enhancer -- thus minimizing skin irritation and other problems frequently associated with

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such compounds -- than would be possible in the absence of ultrasound. The permeation enhancer may be incorporated into the drug medium or it may be applied in a conventional transdermal patch after pretreatment of the body surface with ultrasound.

The present invention may also be used in conjunction with iontophoresis for drugs which are particularly difficult to administer through the skin, i.e., because of the low permeability of the stratum corneum to such drugs. The selected area of the body surface is pretreated with ultrasound and the drug is then administered using conventional iontophoresis techniques.

With respect to skin location, virtually any area of the body surface may be selected so long as it is intact, however, the thickness and permeability of skin at the site of exposure will affect the treatment conditions, i.e., intensity, frequency, contact time, exposure time, and the like. The area of skin through which the drug medium and the ultrasound will be administered can again vary greatly, but will typically be on the order of 1 to 100 cm², more typically on the order of 50 to 100 cm², most typically on the order of 10 to 50 cm².

Example

Based on the present inventors' theoretical analysis of the propagation of ultrasound energy in tissue and the barrier properties of skin, it was concluded that higher ultrasound frequencies might be more effective in enhancing the flux of drug molecules across the skin. This conclusion, based on the assumption that enhancement is proportional to the amount of energy dissipation within the barrier, is supported by Figure 1, which suggests that, within the

first millimeter of skin, ultrasound energy dissipation increases exponentially with frequency.

To test the hypothesis that higher frequencies (>10 MHz) would yield greater enhancement, in vivo experiments were performed on hairless guinea pigs. The setup for carrying out the experiment consisted of a function generator, transducers tuned at different frequencies and a power-meter. ¹⁴C-labeled salicylic acid was used as the "model" marker drug molecule. A saturated solution of unlabeled salicylic acid in water was prepared. Carbopol™ (B.F. Goodrich), a polymer, was added to this solution to make a gel containing salicylic acid at a concentration of 0.57% w/w. This gel was then spiked with a known amount of radiolabeled salicylic acid (approx. 2.27 μ Ci/mg gel). Approximately 30 mg gel per square centimeter of transducer cross-sectional area was then applied to the skin surface of the guinea pigs' flanks. This gel served as both the drug reservoir and the coupling medium between the transducer and skin surface. Frequencies of 1, 7.5 and 16 MHz were tested using an intensity of 0.25 W/cm² and treatment periods (time of exposure of the skin to both drug and ultrasound) of 10 and 20 minutes. At the treatment site, the transducer delivered ultrasound at the appropriate frequency for the designated period. At the control site, in the contralateral flank, the transducer was positioned on the skin, but not activated. Thus, each animal served as its own control.

Enhancement was quantified in two ways: (1) by tape-stripping the outer skin layer at the treatment and control sites immediately after the experimental period (radioactivity in the tape strips was then determined by liquid scintillation counting); and (2) by measuring the

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cumulative amount of ^{14}C excreted in the animals' urine up to 14 hours after initiation of the experiment.

(1) Tape-strip procedure: It has been established that the uppermost layer of skin, the stratum corneum (SC), offers the most resistance to drug penetration. Hence, it was decided to compare the amount of radioactivity present in the SC after ultrasound treatment with that after the control experiment (passive diffusion, no ultrasound). Figures 2, 3 and 4 present a comparison of the total amount of salicylic acid that had penetrated into the SC with 1, 7.5 and 16 MHz exposure for 20 minutes and without exposure to ultrasound. As can be seen, use of 16 MHz resulted in a significantly elevated drug level in the SC as compared to the control. Figures 5 and 6 are comparable to Figures 3 and 4, but here the treatment time was 10 minutes, rather than 20 minutes. Each tape strip removed a certain amount of the SC. Hence, with increasing tape-strip number, tissue further away from the surface was examined. Therefore, a plot of the amount of drug in each strip against strip number reflects the concentration gradient of drug in the SC. Such plots are shown in Figures 7, 8, 9 and 10. The ordinate is the ratio of the amount of radioactivity in the tape-strip after treatment to the amount in the strip after control.

(2) Urinary excretion: To confirm that the amount of drug recovered from the SC reflected the amount of drug penetrated, radioactivity excreted in the urine was monitored. Figure 11 graphically illustrates a comparison of the total amount of radioactivity excreted in urine 14 hours after a 20 minute treatment using 16 MHz and the corresponding control. At least

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five times more drug entered the systemic circulation with ultrasound than without.

5 While the present invention has been described
with reference to specific embodiments thereof, it
should be understood by those skilled in the art that
various changes may be made and equivalents may be
substituted without departing from the true spirit of
10 the scope of the invention. In addition, many
modifications may be made to adapt a particular
ultrasound device, drug, excipient material, process,
process step or steps, to the objective, spirit and
scope of the present invention. All such modifications
15 are intended to be within the scope of the claims
appended hereto.

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CLAIMS

1. A method for sampling physiologic material present beneath a biological membrane comprising increasing the permeability of the membrane by applying ultrasound having a frequency above about 10MHz to a selected area of the biological membrane, at an intensity and for a period of time effective to increase the permeability of the biological membrane and sufficient to enable movement of a diagnostic quantity of the physiologic material through the membrane to a surface thereof and measuring the physiologic material.

2. The method according to claim 1, wherein the physiologic material is measured at the surface.

3. The method according to claim 1 or 2, wherein said period of time is in the range of about 30 seconds to 60 minutes.

4. The method according to any one of claims 1 to 3, wherein said ultrasound frequency is in the range of about 15 MHz to 50 MHz.

5. The method according to claim 4, wherein said ultrasound frequency is in the range of about 15 to 25 MHz.

6. The method according to any one of claims 1 to 5, wherein said period of time is in the range of about 5 to 45 minutes.

7. The method according to claim 6, wherein said period of time is in the range of about 5 to 30 minutes.

8. The method according to claim 7, wherein said period of time is less than about 10 minutes.

9. The method according to any one of claims 1 to 8, wherein said intensity of said ultrasound is less than about 5.0 W/cm².

10 The method according to claim 9 wherein said intensity of said ultrasound is in the range of about 0.01 to 5.0 W/cm².

11. The method according to claim 10, wherein said intensity of said ultrasound is in the range of about 0.05 to 3.0 W/cm².

12. The method according to any one of claims 1 to 11 wherein said selected area is in the range of about 1 to 100 cm².

13. The method according to claim 12 wherein said selected area is in the range of about 5 to 100 cm².

14. The method according to claim 13, wherein said selected area is in the range of about 10 to 50 cm².

15. The method according to any one of claims 1 to 14, including applying to the membrane a coupling agent effective to transfer said ultrasound to the membrane from an ultrasound source.

16. The method according to any one of claims 1 to 15, including applying to the membrane a chemical permeation enhancer.

17. The method according to claim 15, wherein said coupling agent is selected from the group consisting of glycerin, water, and propylene glycol.

18. The method according to claim 15 or 17, wherein the steps of applying the ultrasound and applying the coupling agent are carried out substantially simultaneously.

19. The method according to any one of claims 1 to 18, wherein the ultrasound is applied continuously.

20. The method according to any one of claims 1 to 18 wherein the ultrasound is pulsed.

21. The method according to any one of claims 1 to 20 wherein the membrane is an intact area of the body surface of an individual.

22. The method according to claim 21 wherein the intact area is on the stratum corneum and wherein there is applied to the stratum

corneum a coupling agent effective to transfer said ultrasound to the stratum corneum from an ultrasound source.

Abstract of the Disclosure:

A method for enhancing the permeability of the skin or other biological membranes for sampling of physiologic material is disclosed. In this method, ultrasound having a frequency of above about 10 MHz is used to
5 enhance the rate of permeation of physiologic material through the biological membrane and then a diagnostic quantity of the physiologic material is collected. The method may also be used in conjunction with chemical permeation enhancers and/or iontophoresis.

% of input energy lost in a depth of 1 cm.

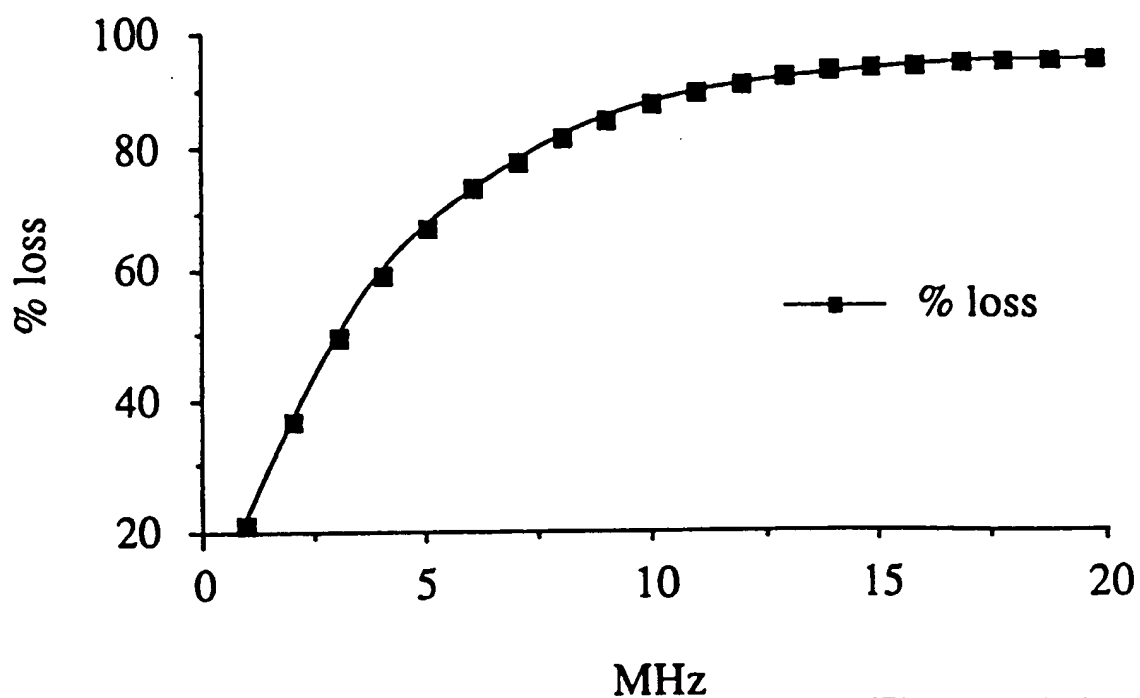


Figure 1(A)

% of input energy lost in a depth of 1 mm.

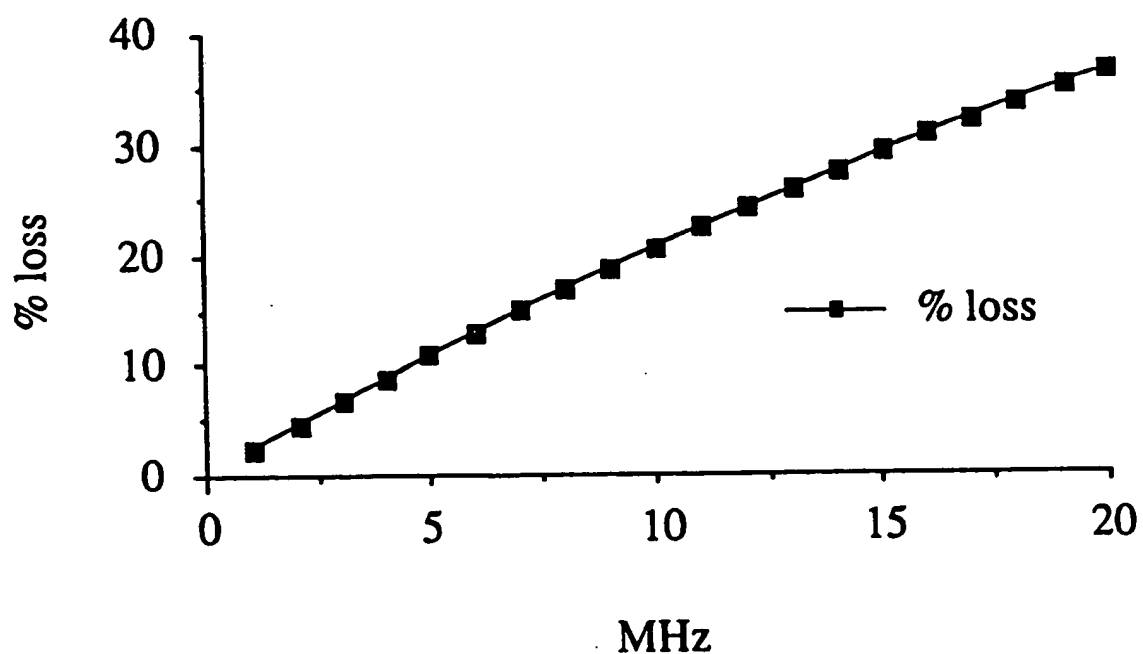


Figure 1(B)

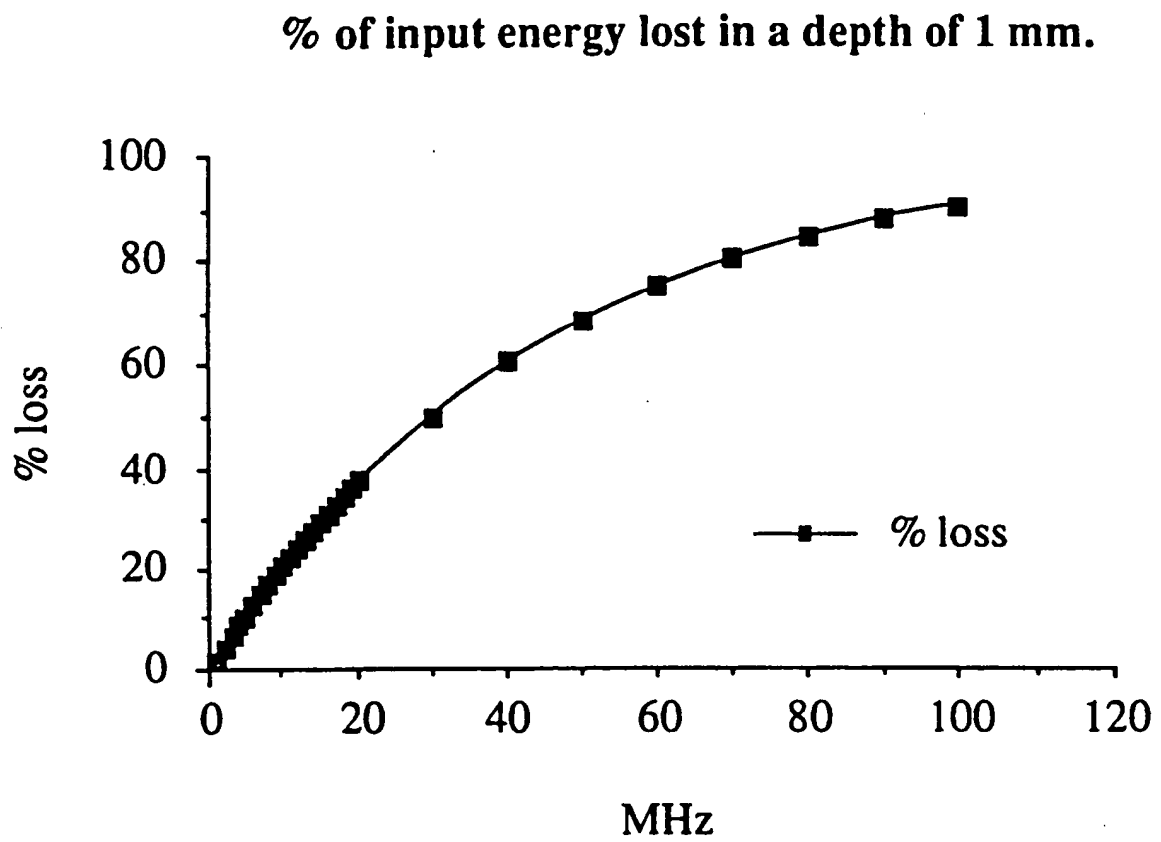


Figure 1(C)

Comparison of the effect of 7.5MHz with control
(20min, 0.25W/cm²)

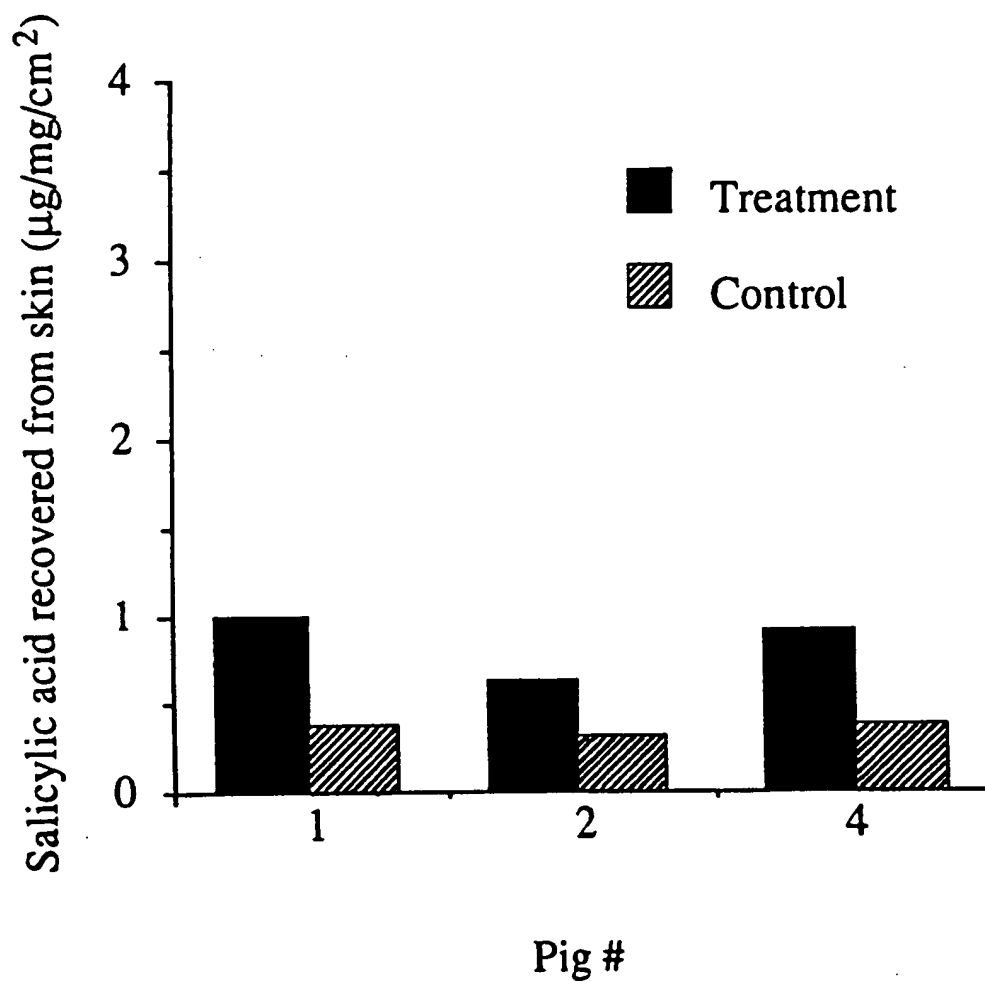
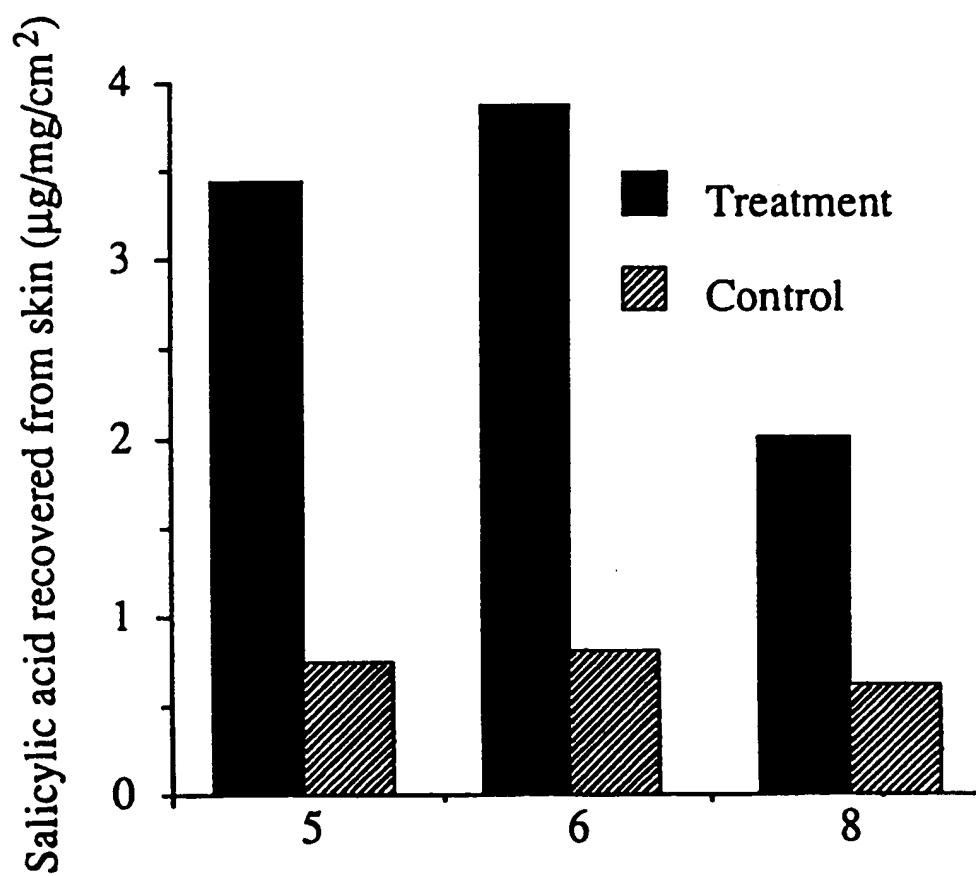


Figure 3

Comparison of the effect of 16MHz with control
(20min, 0.25W/cm²)



Pig #

Figure 4

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Enhancement Ratio ([treatment]/[control]) with 7.5MHz
(20min., 0.25W/cm²)

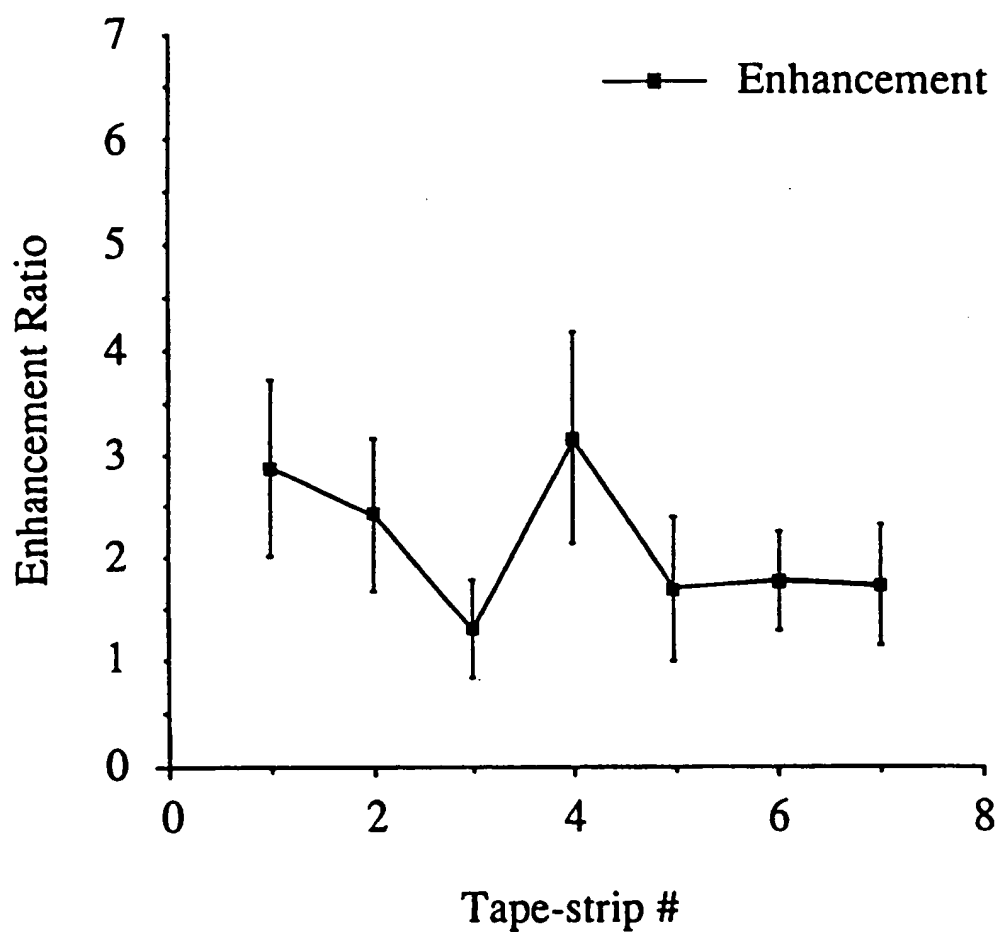


Figure 7

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Enhancement Ratio ([treatment]/[control]) with 7.5MHz
(10min., 0.25W/cm²)

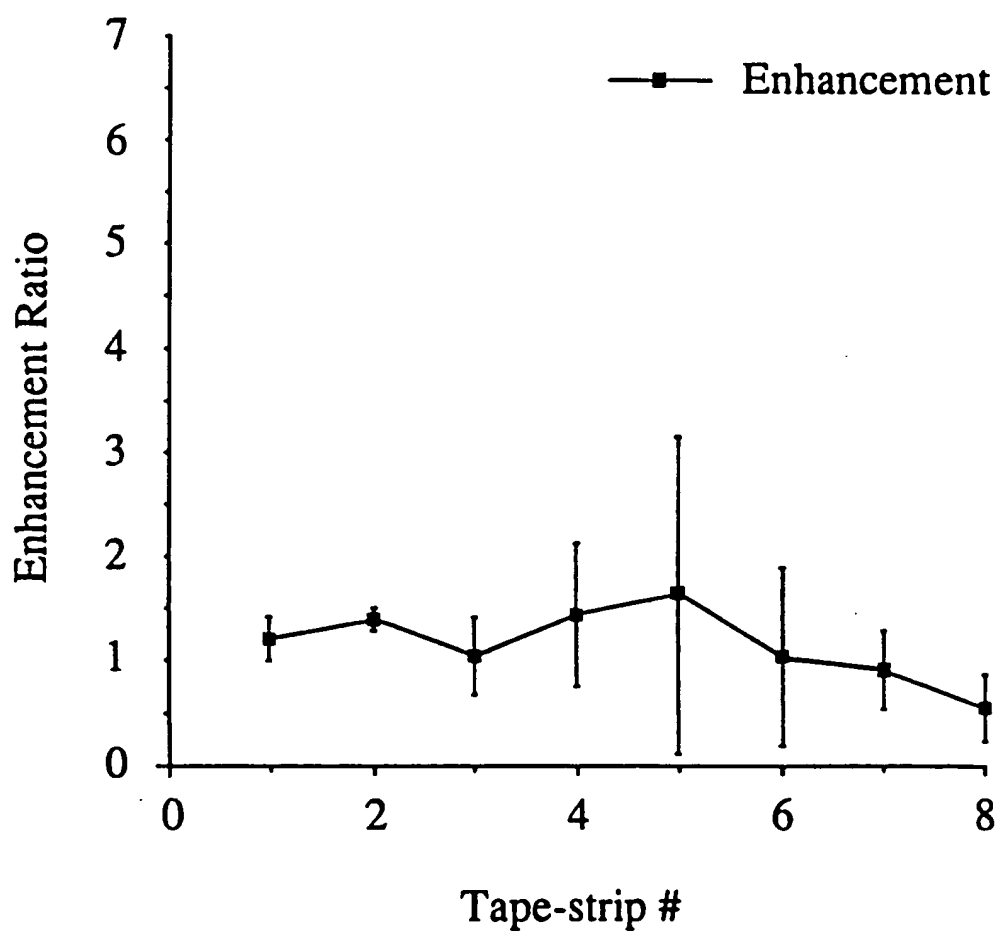


Figure 9

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Enhancement Ratio ([treatment]/[control]) with 16MHz
(10min., 0.25W/cm²)

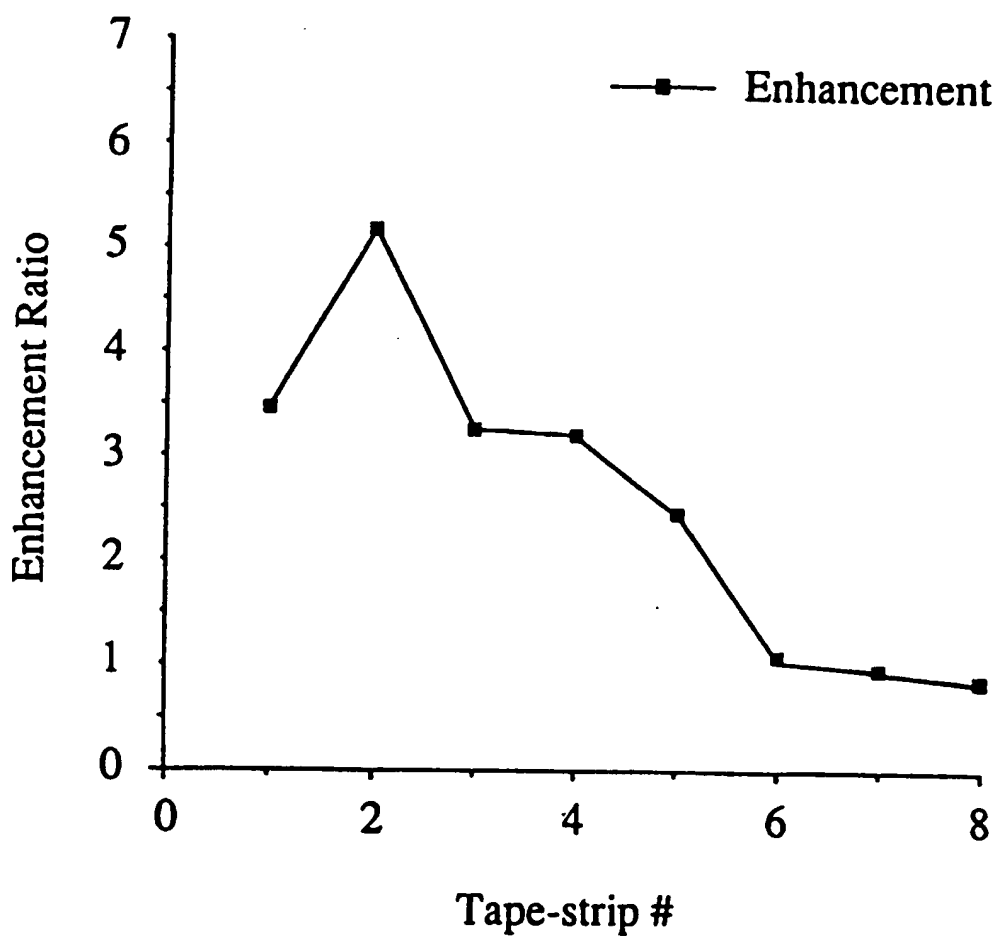
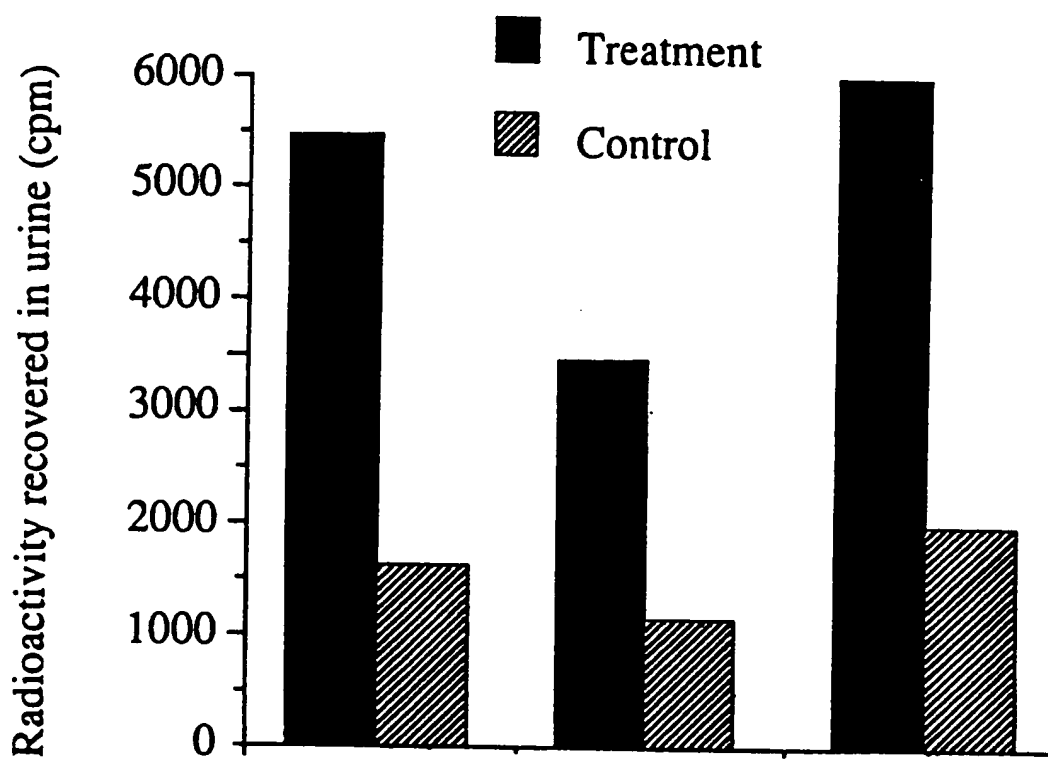


Figure 10

Total radioactivity recovered in urine in 14 hrs. following application of ultrasound (16MHz, 20min., 0.25W/cm²)



Pig #

Figure 11